Assessment of the Need to Perform Life-Saving Interventions Using Comprehensive Analysis of the Electrocardiogram and Artificial Neural Networks

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ABSTRACT

Introduction/Relevance to Symposium

This work addresses the need for advanced medical technologies with a high fielding potential, specifically, development of vital sign monitoring technology.

Rationale

The US Army Combat Critical Care Engineering Task Area aims to improve care in the Battlefield Critical Care Environment (BCCE) by developing new decision support systems that take better advantage of the large data stream available from casualties. In this short review we present new descriptors of physiologic status suitable for decision support in the BCCE. These variables can be extracted from biosignals such as the electrocardiogram (EKG) (featured in this manuscript). They can also be extracted from other waveforms, processed using similar analysis tools. This manuscript reviews our work to date on the development of such decision support systems. We focus on the use of new vital signs derived from heart rate complexity (HRC) and traditional heart rate variability (HRV) analysis in machine learning technology such as artificial neural networks (ANN). We present data from 262 prehospital and emergency department trauma patients, in whom noninvasive vital signs derived from EKG analysis were fed to a commercially available feed-forward back-

Report Documentation Page

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
APR 2010	**N/A**	**-**

4. TITLE AND SUBTITLE
Assessment of the Need to Perform Life-Saving Interventions Using Comprehensive Analysis of the Electrocardiogram and Artificial Neural Networks

5a. CONTRACT NUMBER

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
U.S. Army Institute of Surgical Research 3400 Rawley E. Chambers Ave. Fort Sam Houston, TX 78234 USA

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release, distribution unlimited

13. SUPPLEMENTARY NOTES
See also ADA564622. Use of Advanced Technologies and New Procedures in Medical Field Operations (Utilisation de technologies avancees et de procedures nouvelles dans les operations sanitaires).

14. ABSTRACT
This work addresses the need for advanced medical technologies with a high fielding potential, specifically, development of vital sign monitoring technology. The US Army Combat Critical Care Engineering Task Area aims to improve care in the Battlefield Critical Care Environment (BCCE) by developing new decision support systems that take better advantage of the large data stream available from casualties. In this short review we present new descriptors of physiologic status suitable for decision support in the BCCE. These variables can be extracted from biosignals such as the electrocardiogram (EKG) (featured in this manuscript). They can also be extracted from other waveforms, processed using similar analysis tools. This manuscript reviews our work to date on the development of such decision support systems. We focus on the use of new vital signs derived from heart rate complexity (HRC) and traditional heart rate variability (HRV) analysis in machine learning technology such as artificial neural networks (ANN). We present data from 262 prehospital and emergency department trauma patients, in whom noninvasive vital signs derived from EKG analysis were fed to a commercially available feed-forward back-propagation ANN (NeuralWare, Carnegie, PA). The endpoint was prediction of the performance of life-saving interventions (LSIs) such as intubation, cardiopulmonary resuscitation (CPR), chest-tube placement, needle pneumothorax decompression and blood transfusion. Sensitivity and specificity were explored via construction of receiver operating characteristic (ROC) curves.

15. SUBJECT TERMS

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<tr><td colspan="3">16. SECURITY CLASSIFICATION OF:</td><td rowspan="2">17. LIMITATION OF ABSTRACT
SAR</td><td rowspan="2">18. NUMBER OF PAGES
16</td><td rowspan="2">19a. NAME OF RESPONSIBLE PERSON</td></tr>
<tr><td>a. REPORT
unclassified</td><td>b. ABSTRACT
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Methods

800-beat sections of EKG from 262 patients were analyzed. Sixty-five patients received 88 LSIs (LSI group), which included intubation (n=61), cardiopulmonary resuscitation (n=5), cricothyroidotomy (n=2), pneumothorax decompression (n=16) and blood transfusions (4); 197 did not (NonLSI group). HRC was calculated by several groups of methods to include those which measure (1) the irregularity or randomness of the R-to-R interval (RRI) time series of the EKG; (2) fractal-like correlations within the RRI; (3) symbolic dynamics; (4) signal stationarity. In addition, time- and frequency-domain measures of heart-rate variability were also calculated. The ANN was trained on 70% of the data available for analysis.

Results

Out of 24 available variables calculated from the EKG the ANN chose 14 as independent predictors of LSIs; area under the ROC = 0.86.

Conclusions

Based on EKG-derived noninvasive vital signs alone, it is possible to identify trauma patients who undergo LSIs using ANN with a high level of accuracy. Some HRC methods such as point correlation dimension can be applied to real-life, noisy EKG and provide important information about the injury severity of casualties. Validation of these new descriptors of physiologic status and development of real-time monitoring platforms is under way in our laboratory in multiple research settings.

1.0 INTRODUCTION

Implementation of new decision support systems on the Battlefield Critical Care Environment (BCCE) could significantly enhance medical decision making leading to improvements in outcome. These new tools could be developed by taking advantage of the vast information stream from casualties in the BCCE. At present, decision making at any echelon of care is based on old practices including visual inspection of the patient and intermittent assessment of time-averaged vital signs. Whereas these tools are easy to use when direct contact with the patient is possible their utility in timely and sensitive assessment of injury severity is limited and frequently leads to errors in diagnosis (1). For example in one recent study 23% of trauma patients with normal vital signs required a life saving interventions (2). Furthermore, the intermittent discrete nature of traditional vital sign acquisition and frequent changes in providers along the echelons jeopardizes the continuum of care leading to loss of information about the casualty. By contrast, decision support via continuous assessment and documentation of the patients' status from point of injury to the last echelon of care with comprehensive assessment of status, storage of history and trends, if achieved, would significantly enhance the diagnostic capabilities of providers at BCCE. One element of such decision support system involves retrieval and processing of information from available sensors. In this short review we present new descriptors of physiologic status suitable for decision support in the BCCE. These variables can be extracted from biosignals such as the electrocardiogram (EKG) (featured in this manuscript) or other waveforms, processed using similar analysis tools as presented here. The resulting panel of descriptors could be processed in association with other information available to or generated by providers and analyzed in real time via machine learning algorithms, such as artificial neural networks. The ultimate goal of this effort is to develop information-driven decision support systems that will equip providers with actionable *information* not more *data* to be interpreted.

2.0 NEW DESCRIPTORS OF PHYSIOLOGIC STATUS FOR DECISION SUPPORT

2.1 Heart Rate Variability

The need for new descriptors of physiologic status as candidate variables for decision support systems has motivated a search for non-invasive correlates of injury severity extracted from available signals, such as the electrocardiogram (EKG), blood pressure, oxygen saturation, respiratory rate, or other sensor-derived waveforms. One common approach to signal analysis commonly applied to the EKG, called frequency-domain analysis, uses fast Fourier transform (FFT) or similar methods applied to the R-to-R interval (RRI) time series to quantify the strength of the regular oscillations present in it. Two of the key metrics derived from FFT are the high-frequency power (HFP) and low-frequency power (LFP) of the periodic oscillations in the EKG. Respiratory sinus arrhythmia (RSA)—an oscillation that occurs at the same frequency as the respiratory rate--has been shown to be a major component of HFP and is attributed to actions of the parasympathetic (vagal) nervous system (3,4). The LFP metric is less specific and has been related to both sympathetic and parasympathetic autonomic activity (3,4). Accordingly, an EKG which features a pronounced RSA measured as slowing of the heart rate after exhalation relative to the heart rate during inspiration is a sign of normal vagal activity and results in an elevated HFP, compared to an EKG which varies little. HFP and LFP, along with time-domain measures (simple statistics such as mean RRI, standard deviation RRI, etc.) are the main tools in the panel of methods collectively called heart rate variability (HRV) analysis. To summarize, HRV refers to a collection of methods describing regular periodic oscillations in the heart rate, attributed to the vagal and/or sympathetic branches of the autonomic nervous system.

It is important to specify the particular metric by which HRV is investigated in any given case rather than mention that HRV “increased” or “decreased”. These semantics are necessary to avoid confusion between changes in HRV findings and changes, e.g., in mean heart rate. This is a misconception because the mean heart rate may stay high during vagal withdrawal, or low during vagal oversaturation, yet the HRV metrics reflecting vagal modulation to the heart may be nearly zero (5). Furthermore, HRV may “increase” as measured by one metric and decrease or not change by another. In general all HRV metrics are characterized by high inter-individual variability, as the autonomic nervous system is very responsive to sensory stimuli. Thus, more precisely, HRV metrics should be viewed as a collective panel of metrics linked back to branch-specific autonomic input. As with any analysis method careful consideration of methodological limitations of HRV must be in place before application to human monitoring (4,6,7).

Capitalizing on the potential of HRV to provide non-invasive insight into the autonomic nervous system actions during various conditions, Winchell and Hoyt showed that low HRV—specifically, sympathetic input to the heart (measured by LFP)—is associated with mortality in critically injured intensive care unit patients (8). This finding reiterates the long-standing clinical suspicion that during shock, humans compensate by increasing their heart rate, which is primarily modulated by sympathetic input to the heart. Patients in whom such compensation is inadequate or exhausted show low sympathetic activity and may die. Similarly, Cooke et al. showed that low sympathetic input to the heart is associated with mortality in prehospital trauma patients (9) and that this analysis may be suitable for remote triage (10).

FFT-based methods such as those used in the above studies, however, require the analyzed data to be very stationary (i.e., change little around a mean value, see section Technical Obstacles below). In addition, FFT-based measurements of parasympathetic activity with the HFP metric depends heavily on respiratory activity, since the power spectrum will shift significantly as breathing rate and depth change (11). This mandates assessment of respiration concomitantly with ECG analysis. A significant methodological limitation is that FFT-based methods say little about nonlinear patterns in the EKG and inter-organ interactions. These and other caveats (5,7,12) notwithstanding, FFT-based techniques, when used within their methodological constraints, could be useful for comprehensive analysis of waveforms because they provide branch-specific insight into the autonomic nervous system. Thus, HRV refers to a collection of methods that could be useful for obtaining additional specific information about compensation in the injured such as, for example, assessment of the fast-acting vagal influences on beat-to-beat cardiovascular regulation. This is the more consistent and reliable measurement available from HRV analysis.

2.2 Heart Rate Complexity

A different approach to signal analysis uses statistical methods derived from nonlinear dynamics that, broadly speaking, quantify signal patterns or structural complexity of the RRI time series. They also quantify short- and long-term memory effects (correlations) in the signal (13-17). *Structural complexity* of the signal is taken to be a reflection of the *regulatory complexity* and organ system interconnections (18-20). Nonlinear methods are applied within the framework of a complex systems approach to human physiology and serve as a toolset for investigation of complex inter-organ interactions in the body (21). Nonlinear methods here are broadly termed here heart rate complexity (HRC) analysis, which denotes a family of tools that measure the amount of regulatory feedback acting, in this case, on the cardiovascular system. HRC has previously been used for EKG analysis in experimental and clinical settings by others (15,17,22-25) as well as by us (20,26-29). These studies show that reduction of HRC is a sensitive indicator of physiologic deterioration and is a new nonspecific descriptor reflecting overall cardiovascular "health" potentially suitable for decision support in the BCCE (19,20,29).

We previously applied HRC analysis in animals with hemorrhagic shock. By analysing ectopy–free sections of EKG we found that hemorrhage causes a decrease in the irregularity of the RRI time series as measured by an HRC metric, entropy (26). In this area of research, entropy is different from the classical thermodynamic definition. Rather, entropy in the information theory sense means that higher entropy is associated with more information in the system, and vice versa (30). Entropy can be measured by several approaches (16,22,31). We used approximate entropy (ApEn) (31) and sample entropy (SampEn) (16). These metrics are computationally somewhat distinct, with SampEn being more suitable for analysis of shorter time series (16,20). Entropy is calculated as the negative logarithm of the conditional probability of finding arbitrarily similar patterns in the data. Pattern similarity is defined as sub-epochs of data being "mathematically close" at the next iteration and within a proportion of the standard deviation of the data set. Regular data sets have high conditional probabilities and low entropy. Data sets that are more random or irregular are less predictable and high in entropy. A more irregular dataset is higher in entropy, contains more information in the system, is under control by multiple feedback loops, and denotes higher heart rate complexity (HRC).

Complexity and variability are not necessarily the same. A periodic sinusoidal signal can be variable, manifested by increased HRV, but not complex. This is because variability may be caused by activity in a single feedback loop. Vice versa, a more random signal can be less variable and highly complex (15). HRC as measured by entropy decreases with aging and disease (15). When critical states occur, regulatory feedback may be withdrawn thus decreasing entropy and HRC (13,32). We established in anesthetized swine that blood loss led to a decrease in SampEn which was reversed with resuscitation, as shown in Figure 1 (33).

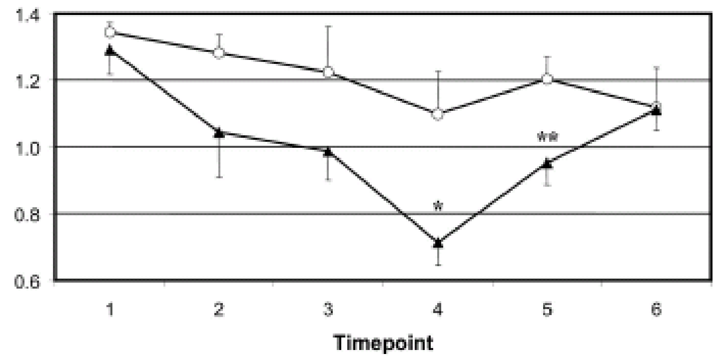

Figure 1: Open circles represent control swine which were anesthetized and mechanically ventilated. The black triangles show the injury group that underwent a step-wise 30 ml/kg blood loss, exhibiting statistically significant sample entropy (SampEn) differences between groups indicated by the asterisks. The y-axis denotes SampEn in arbitrary units, and the x-axis denotes time points during blood loss 1 through 4 and resuscitation with lactated Ringer's solution (time point 5) and reinfusion of withdrawn blood (time point 6).

We further investigated changes in HRC in patients undergoing post-burn resuscitation (28). The study demonstrated that during burn shock and before resuscitation, SampEn is low and then increases with volume restoration (Fig. 2) (28).

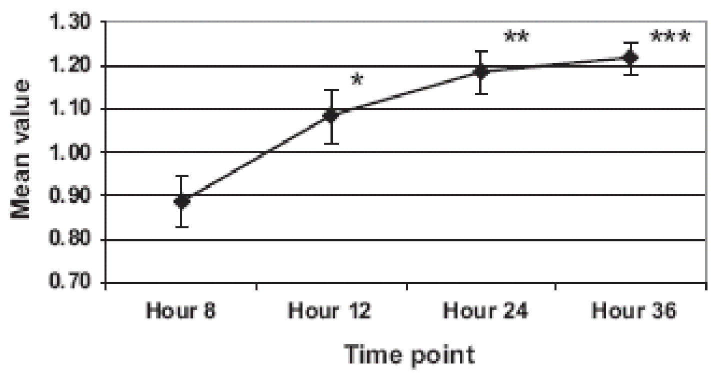

Figure 2: The y-axis denotes SampEn in arbitrary units, and the x-axis denotes ongoing resuscitation in hours for post-burn incident in humans, with statistically significant differences from initial SampEn indicated by asterisks.

In another study in prehospital trauma patients during transportation to a level I trauma center, we found that decreased HRC, measured via several complementary methods which included entropy, correlates with death (19). Furthermore, in that study, which involved off-line analysis of EKG sections collected during helicopter transport, none of the traditional vital signs or FFT-based HRV metrics distinguished eventual survivors from non-survivors; whereas several of the HRC metrics did (19). That retrospective study demonstrated that HRC is a more sensitive injury severity assessment tool when compared to traditional vital signs or HRV-derived descriptors. Among the calculated EKG-derived HRC metrics, entropy (ApEn, calculated over longer time segments e.g. 800 heartbeats) and a signal distribution metric which describing the degree of narrowness of data pattern distributions around the mean were highly associated with mortality (Fig. 3).

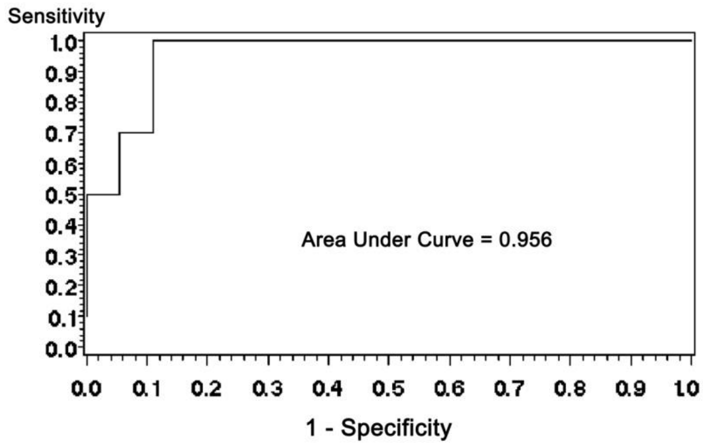

Figure 3: Receiver-operating characteristic curve (AUC) of a model based on EKG-derived HRC metrics (ApEn and Dis_2), which were found to be highly associated with mortality without any other information from traditional vital sign or data available from direct contact with the injured. Model equation: P (mortality) = $e^k/(1 - e^k)$, where k = 9.91 – 14.78 * (ApEn) + 0.02 * (Dis_2). AUC = 0.956 (95% CI = 0.86 – 1.0). Dis_2 is symbolic dynamic metric obtained by transformation of the RRI signal to a sequence of “words” composed of symbols each of which represents a probability distribution of patterns within the RRI values in reference to the mean and deviation from the mean.

Furthermore, when a variable retrievable during direct examination of the patient (the motor component of the Glasgow Coma Scale) was added to the model, the entropy measure of HRC remained in the model (Fig. 4).

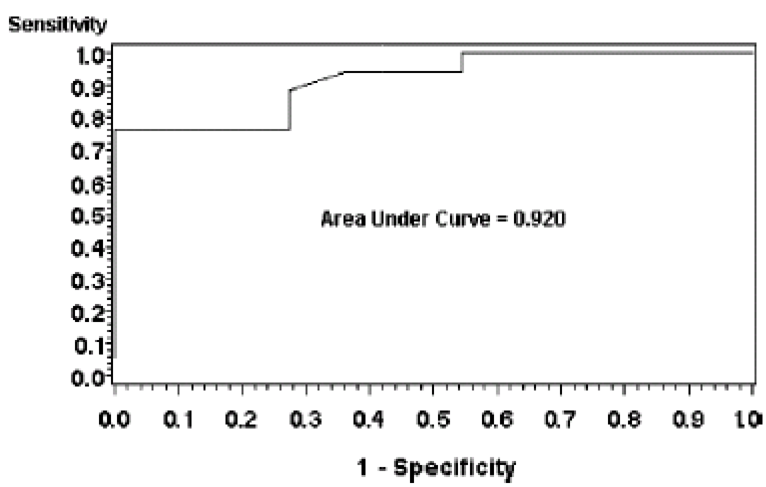

Figure 4: Receiver-operating characteristic curve (AUC) of the model based on EKG-derived descriptors of status combined with information from hands-on assessment of the casualty represented by the motor component of the Glasgow Coma Scale score (GCSm). Model equation: P (mortality) = $e^k/(1 - e^k)$, where k = 14.95 – 10.92 * (ApEn) + 0.87 * (GCSm). AUC = 0.92 (95% CI = 0.80 – 1.0).

As seen in the above figures entropy remained in the predictive equation in both stages of modelling, signifying that HRC carries additional independent information about casualty status not reflected in any of the traditional vital signs or commonly used injury assessment scores such as GCSm (19). In the above studies the HRC metric ApEn was highly correlated (r=0.99) with SampEn and was used instead of SampEn in the logistic equations. To re-iterate, both metrics are methodologically similar. We since moved to using SampEn as our main HRC irregularity metric because it is less sensitive to dataset length than approximate entropy; the latter requires 800 data points for a valid result (31). SampEn on the other hand allows accurate assessment of irregularity in a time series that is only 100 to 200 heartbeats long (20). It also provides for a more reliable measure of irregularity in noisy signals, potentially suitable for continuous real-time applications (22).

In a follow-up study, we considered a more practical diagnostic endpoint than mortality; namely, the performance of life-saving interventions (LSI)s such as intubation, chest tube placement, cricothyroidotomy, or cardiopulmonary resuscitation (2). Decreased HRC as measured by SampEn and other complementary metrics were associated with the performance of LSIs in prehospital trauma patients (29).

It is noteworthy that in neither of the above studies did heart rate or blood pressure values distinguish surviving patients (19), or patients who received LSIs (29), reiterating that conventional vital signs alone are inconsistent markers of critical states in humans (1). In a recent report we found HRC to provide additional information to conventional vital signs as manifested in a significant improvement in the area under the curve exploring association with the need to perform LSIs. Namely, the area under the curve based on heart rate and blood pressure data alone was 0.69 whereas it increased to 0.86 with addition of a few key HRC metrics and further to 0.95 after addition of all HRC and some HRV metrics to the model (34). This reiterates the concept of comprehensive assessment of patient status using complementary tools from HRC and HRV analysis (27-29,33,35). Since no single metric is likely to provide a complete picture of a patient's status, comprehensive analysis using multiple descriptors has the potential to increase validity and reliability of findings.

The same analyses approaches as described for EKG can be used to other sensor-derived data such as respiratory waveforms. We demonstrated this capability in a recent study in which we utilized SampEn to investigate differences in the irregularity of inter-breath period between spontaneously breathing patients on continuous positive airway pressure (CPAP) vs. volume-controlled mechanically ventilated patients (VC). We carried out SampEn analysis utilizing 200 inter-breath periods following the same concepts described above for EKG analysis. This study demonstrated that VC patients have more regular breathing patterns compared to CPAP patients (36). More importantly, presence of more irregular (complex) breathing patterns during spontaneous breathing trials was associated with successful extubation, whereas patients with less irregular (less complex) inter-breath periods failed extubation (36).

HRC is less specific than HRV in the sense that specific autonomic correlates of HRC have not been identified. To this end, vagal activity appears to be a consistent component of HRC. In studies by others (24,37)as well as us (19,20,26), changes in HRC as measured by various complementary nonlinear metrics were unidirectional with the HRV metric HFP. The nonspecificity of HRC is not surprising considering that HRC quantifies the overall amount of regulation present in a system, rather than the activity of a single feedback loop. This is why we propose to use HRC as a way to assess the overall "health" in a complex system such as a critically injured patient.

3.0 MACHINE LEARNING FOR MULTIVARIATE ANALYSIS

Generation of multiple descriptors from traditional vital signs, HRC, and HRV raises the problem of how best to use them in decision support systems. An established approach to a multivariate problem like this is machine learning (ML).

Clinical decision making by physicians is a complicated, subjective, and nonlinear process. More objective tools stemming from advances in artificial intelligence are now available for medical prognosis (38) and have been used with encouraging results (39,40). Some examples of ML-based classification using artificial neural networks (ANNs) exist in the literature. These include decision support for (1) extubation of infants on mechanical ventilation (41) (2) admission of patients with chest pain (39), (3) classification of colon cancer and prediction of survival (42), and (4) prediction of survival after trauma (40,43). This growing interest in using ML can be explained by the ability of neural networks to "learn" and "adapt" directly from data, thus accommodating the intrinsic nonlinear nature of biomedical data (38). Other classification methods such as decision trees, linear discriminant analysis, and support vector machines are available for evaluation in this application. Our team compared several ML-based approaches, with the aim of providing an estimate of the probability of LSIs in trauma patients (44). A real-time ANN implemented on a mobile PC showed a 92.3% accuracy in cumulative assessment of the need to perform LSIs based on of vital sign and demographic information retrieved from 2170 trauma patients (44).

Most studies performed to date that involved ML, however, utilized large numbers of input variables--to include demographic data, disease symptoms, laboratory findings, and injury severity scores. Generation of this amount of information is time-consuming, requires direct contact with the patient, and presumes presence of equipment not available in the field. Alternatively, we proposed ML analysis of EKG-derived metrics (45). For this purpose, we used EKGs collected from prehospital trauma patients in the U.S., together with combat casualties admitted to an emergency department in the Iraq combat zone (35). Sections of EKGs were acquired from these patients and analyzed using multiple HRC and HRV methods. Information about LSIs was acquired from patient charts. The calculated descriptors of status were submitted to a commercial ANN and were found to be highly associated with the need to perform LSIs. Figure 5 depicts the sensitivity and specificity of the ECG-derived metrics for performance of LSIs using receiver operating characteristic (ROC) curve. This result was achieved with information from 14 EKG-derived HRC and HRV descriptors (Fig. 5).

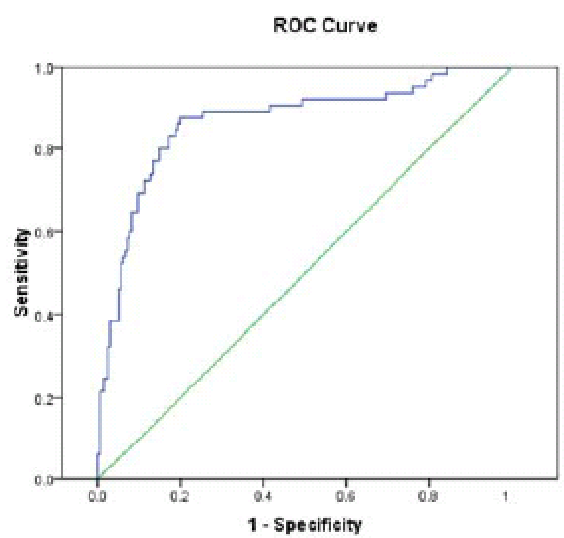

Figure 5: ROC curve for model derived by ANN exploring association with LSIs using EKG variables alone. Area under the curve (AUC) = 0.868; 10-fold cross validation; standard error 0.028. Asymptotic significance was 0.001, and the lower and higher asymptotic 95 % confidence intervals were 0.812 and 0.924, respectively.

Based on these results, we consider automated processing and classification of the information contained in the new descriptors of injury severity derived from EKG an attainable task. By evaluating the available EKG (or other waveform)-derived descriptive information with additional demographic or vital sign data, such decision support systems will enhance medical decision making.

In summary, previous research and our work in particular show that detection of cardiovascular perturbation and prediction of the need to perform LSIs could be significantly improved. The proposed HRC measures and decision support algorithm are expected to be implementable in real time, pending resolution of some technical obstacles.

4.0 TECHNICAL OBSTACLES

At present, there are several obstacles that need to be overcome before successful implementation of sensor-based descriptors of physiologic status can be expected in real-time. The first well-known obstacle is data quality and the amount of "electromechanical noise" in any waveform to be analyzed. For EKG, disconnection of leads, acquisition (digitization) rate and mechanical artefacts of any kind have been shown to render traditional HRV analyses useless. This means that accurate identification of EKG fiducial points is a hallmark of reliable waveform processing (6). Effects of these factors on nonlinear analysis tools are less well documented. Although nonlinear analysis tools are often cited as "robust to noise," no method is likely completely immune to missing or corrupted data. One way of dealing with noisy data is to analyze shorter clean data sets and obtain a "snapshot" of the casualty status (20). However, for continuous analysis of real-time data, reliable signal quality assessment tools will have to be developed and validated (46-48).

A second obstacle is presence of "organic noise" or biological artefacts, due to premature beats or arrhythmias that can significantly alter the results of waveform analysis as they introduce sudden changes into the signal distribution. We distinguish this "organic noise" from the above "electromechanical noise" because various forms of arrhythmias carry independent prognostic value and can quantified by methods such as heart rate turbulence (49,50). Sudden changes in the RRI affect the stationarity of the signal, and maybe undistinguishable from an undetected beat due to poor performance of the EKG R-wave detector. Thus stationarity may be altered due to changes of cardiac origin as well as due to detection errors.

Regardless of the specific cause, a stationary signal is one its mean value remains relatively constant in relation to the standard deviation of the signal over some period of time. This measure is always relative to the time segment over which analysis is being considered. The longer the signal segment, the less stationary it is. This suggests that more reliable results could be obtained if shorter segments of data are analyzed. From a practical standpoint, given the consideration of dataset length, obtaining a "snapshot" of the casualties' condition may be a viable diagnostic solution in the BCCE if a continuous data stream cannot be obtained (20).

Changes in fundamental signal properties such as nonstationarity can by themselves serve as descriptors of status (51). If stationarity is not accounted for, a danger exists that changes in the descriptors calculated from the signal are solely caused by rapid changes in data character (stationarity) rather than true changes in dynamics of the data (22). We consistently use an index of nonstationarity in our studies and monitor changes therein (20,27). Nonstationarity render traditional HRV analyses useless because a single spurious peak (whether true ectopic beat or spurious detection) can profoundly influence the spectral components of HRV (6). Nonstationarity can also significantly skew most nonlinear analysis results. However, several approaches have been reported to be less sensitive to nonstationary changes in the data such as the point correlation dimension (PD2i, see next section) (23,52), quadratic sample entropy (22) or non-Markov stochastic methods (53). In addition, methods like empirical mode decomposition may be one way of preprocessing of data before analysis (54).

A third caveat is the need for common communication protocols between existing monitoring equipment manufacturers. This is an important roadblock that hampers implementation of new analysis methods on existing monitoring platforms. Overcoming this roadblock will require collaboration among researchers in the medical, signal processing, biomedical engineering and computational biology fields in order to improve combat casualty and civilian trauma care (55,56). The commercial success of the cardioverter-defibrillator industry clearly demonstrates that the obstacles at hand can be successfully overcome.

4.1 Does HRC Work in Real-Life Noisy Data?

One of the methods reportedly designed to deal with nonstationary RRI data sets is the point correlation dimension (PD2i, Vicor Inc., Boca Raton, FL) (23,57). The Correlation Dimension concept models the cardiovascular system as a stationary strange attractor, plots its position in phase space and quantifies a decrease in the dimensions of regulation of this system as a decrease in the number of states of the system in phase space.(23) Thus, a more complex signal is a reflection of a higher number of dimensions of regulation or feedback loops in action, whereas a lower correlation dimension points to a decreased complexity of regulation. PD2i is thought to measure the degree of interaction or "cooperation" among the various feedback loops that control the heart rate (23,57) PD2i has been applied in animal(23,58) and human studies;(57,59) and was found to separate patients at risk of lethal arrhythmias.(59,60) The algorithm is currently FDA approved as a tool to measure autonomic status in humans.

In a recent study a blinded analysis of unprocessed ("Raw") EKG segments from trauma patients obtained from the USAISR Trauma Vitals database was performed.(61,62). This work was conducted to investigate the potential of PD2i to be applied to "real world" data which contain noise or ectopy, and which consist of data sets of varying lengths. The analysis was performed using proprietary software (Vicor 2.0, Vicor Technologies, Inc., Boca Raton, FL) that takes the EKG as an input, determines the RRIs, employs several noise analyses, and then calculates the PD2i (23,58,63). A PD2i value of 1 is considered a critical cut-off value in that if it was lower the condition of the subject was likely critical. PD2i calculations were carried out in unprocessed "Raw" files which contained EKGs of various lengths (mean 21 minutes, range 2.7 to 81.1 minutes) and were not preprocessed manually. These results were compared to those obtained from files that were previously processed in our laboratory and verified to have no ectopic beats or spuriously detected EKG. These "Clean" data sets were 200 beats in length and were selected from within the longer "Raw" data sets. Results of the analysis of Raw files, exploring associations between PD2i score and 3 outcome measures (the need to perform LSI, Death, and Death or LSI), are summarized in Table 1. LSIs included intubation, cardio-pulmonary resuscitation, chest tube placement and cricothyroidotomy.

Table 1: Results of the Analysis of Raw Files.

Raw analysis	Sensivity	Specificity	AUC
• LSI	• 85.2%	• 53.6%	• 0.704
• Death	• 90.0%	• 51.2%	• 0.689
• Death or LSI	• 87.5%	• 50.3%	• 0.672

The results showed that critically low PD2i values were associated with performance of LSIs and death in trauma patients. Furthermore, results obtained from Raw vs. Clean files showed reasonable agreement in calculated PD2i values especially in the important diagnostic range of PD2i=1 (Fig. 6).

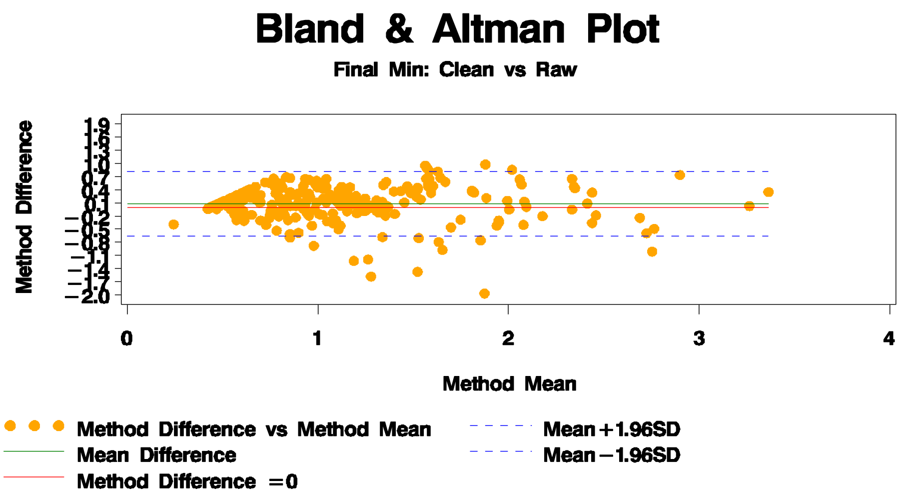

Figure 6: Bland-Altman plot depicting correspondence between PD2i calculations in the Raw and Clean files.

We concluded that PD2i applied to unverified EKG data may provide information about the status of trauma patients and may be a useful tool for assessment of injury severity and the need to perform LSIs. Based on these preliminary results, technology like PD2i could be a useful component of decision support, as it could identify injury severity in EKG files of questionable quality. In addition, insofar as PD2i is a multi-scale metric, it is conceptually similar to multiscale entropy (MSE). The latter involves coarse-graining of the RRI time series, and measures SampEn along multiple time scales (64). Preliminary data from our laboratory suggests that use of these multiscale metrics may provide even more accuracy in detecting the severely injured (65).

5.0 CONCLUSIONS

This review covered recent work in generating new descriptors of injury severity from common physiologic signals such as the EKG, with the aim of developing decision support tools. We advocate for a comprehensive use of various tools from HRV analysis which provide more specific information about autonomic compensation, and from HRC analysis which serves as a more sensitive and comprehensive marker of overall health of casualties. Processing of the multiple descriptors of patient status could be automatically carried out using various machine learning approaches such as ANN, thus avoiding information overload. Some obstacles remain to be solved, including data quality, artefact detection, storage, and inter-device communication. However, several methods show low sensitivity to data quality problems, and produce relevant and usable information even at the current stage of development. This increases our enthusiasm about expedient resolution of the challenges at hand. It is imperative that as we carry this research to clinical trials, we work together in multidisciplinary teams to take advantage of advances in the cardiovascular device industry; to improve data capture, storage, compression and transmission; and to incorporate these new descriptors of physiologic status into meaningful decision-support systems suitable for daily clinical use.

ACKNOWLEDGMENTS

The authors are grateful to James Skinner, Corina Necsoiu, Kerfoot Walker III, Bill Baker, John Ward, John Jones, Michael Lucas, Ruth Nguyen, and Rachael Dimitri for assistance with data collection and analysis.

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